REFERENCES

AHLENIUS, S. & ENGEL, J. (1971). *Eur. J. Pharmac.*, **15**, 187–192.
AHLENIUS, S. & ENGEL, J. (1973). *J. Pharm. Pharmac.*, **25**, 172–174.
ANTELMAN, S. M. & SZECHTMAN, H. (1975). *Science*, **189**, 731–733.
CARLSSON, A. & LINDQVIST, M. (1963). *Acta pharmac. tox.*, **20**, 140–144.
CARLSSON, A., PERSSON, T., ROOS, B. E. & WALINDER, J. (1972). *J. Neural Transmission*, **33**, 83–90.
CARLSSON, A., ROOS, B. E., WALINDER, J. & SKOTT, A. (1973). *Ibid.*, **34**, 125–132.
CORRODI, H., FUXE, K., HAMBERGER, B. & LJUNGDAHL, A. (1970). *Eur. J. Pharmac.*, **12**, 145–155.
KEBABIAN, J. W., CLEMENT-CORMIER, Y. C., PETZOLD, G. L. & GREENGARD, P. (1975). In: *Advances in Neurology, vol. 9*: Dopaminergic Mechanisms, p. 1–11. Editors: Calne, D., Chase, T. N. & Barbeau, A. New York: Raven.
MATTHYSSE, S. (1973). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **32**, 200–205.
SPECTOR, S., SJOERDSMA, A. & UDENFRIEND, S. (1965). *J. Pharmac. Exp. Ther.*, **147**, 86–95.

The involvement of serotoninergic and noradrenergic systems in the compulsive gnawing in mice induced by imipramine and apomorphine

N. K. DADKAR, A. N. DOHADWALLA, B. K. BHATTACHARVA, *Department of Pharmacology, Research Centre, Hoechst Pharmaceuticals Ltd., Muland, Bombay 400 080, India*

Antidepressant agents such as imipramine and amitriptyline alter the effect of apomorphine from running and licking to intense gnawing behaviour in mice, which has been termed as "potentiation" (Pedersen, 1967). This action was considered due to enhancement of dopaminergic and inhibition of cholinergic systems in the central nervous system (Pedersen, 1967, 1968). Imipramine has been shown to block both 5-hydroxytryptamine (5-HT) and noradrenaline uptake at the neuronal levels (Carlsson, Corrodi & others, 1969). Friedman, Shopsin & others (1974) have shown that serotoninergic rather than adrenergic neuronal systems are involved in the antidepressant effects of imipramine. These results suggest that both catecholamines and 5-HT may play an important role in the compulsive gnawing syndrome produced by apomorphine in combination with imipramine.

The present studies were, therefore, designed to re-evaluate the importance of serotoninergic and adrenergic systems in the imipramine-apomorphine induced gnawing behaviour, by using various agents known to modify synthesis and storage of 5-HT and noradrenaline.

The gnawing activity was measured in mice of either sex, 19–21 g, in groups of 6, in a cage with corrugated paper covering the floor (Ther & Schramm, 1962). After administration of the test substance intraperitoneally, apomorphine (10 mg kg^{-1}) was injected subcutaneously at varying intervals. Imipramine (60 mg kg^{-1}) was injected 15 min before apomorphine. The bites in the paper caused by gnawing were counted for 10% of the total surface and the mean and s.e. of at least 6 groups of animals per test compound were calculated.

Table 1. *The effect of pretreatment with various pharmacological agents on the potentiation of apomorphine gnaw compulsion by imipramine (60 mg kg^{-1} i.p.).* The values in the parentheses represent the number of groups, each containing 6 mice. The results were compared statistically using Student's *t*-test.

Treatment	Dose (mg kg^{-1}, i.p.)	Pretreatment* time in h	Mean % area gnawed ± s.e.
Saline	—	—	73 ± 2·0 (15)
Methysergide	10·0	0·5	12 ± 5·8 (6)***
PCPA	3 × 100 (3 days)	last dose 20·0	39 ± 4·6 (9)***
Haloperidol	1·0	2·0	9 ± 3·5 (9)***
FLA-63	40·0	2·0	0 (6)***
Phenoxybenzamine	30·0	0·5	0 (6)***
Tetrabenazine	20·0	1·0	5 ± 1·2 (12)***

*** Significantly different from control, $P < 0.001$.
* Pretreatment time before apomorphine. Imipramine was injected 15 min before apomorphine (10 mg kg^{-1}, s.c.).

Our observations are in agreement with the previous results of Pedersen (1968), that imipramine in combination with apomorphine (10 mg kg^{-1}) exhibited intense gnaw compulsion, while apomorphine (10 mg kg^{-1}) alone did not show such activity. The results are summarized in Table 1.

Pretreatment with the 5-HT antagonist, methysergide (10 mg kg^{-1}) and tryptophan hydroxylase inhibitor, *p*-chlorophenylalanine (PCPA) (100 mg kg^{-1} for 3 days), significantly reduced ($P < 0.001$) the potentiation of apomorphine gnawing compulsion. These results support the view that serotoninergic systems play a significant role in imipramine-apomorphine gnawing behaviour.

Haloperidol (1·0 mg kg^{-1}), a central dopamine receptor antagonist, FLA-63 [bis-(4-methyl-1-homopiperazinylthiocarbonyl)-disulphide] (40 mg kg^{-1}), an inhibitor of dopamine-β-oxidase and phenoxybenzamine (30 mg kg^{-1}), a central noradrenaline receptor antagonist were shown to reduce significantly ($P < 0.001$) the potentiation of apomorphine gnawing. Tetrabenazine has been shown to deplete selectively central noradrenaline and 5-HT stores (Quinn, Shore & Brodie, 1959; Pletscher, Brossi & Gey, 1962). In this study tetrabenazine (20 mg kg^{-1}) inhibited the intensity ($P < 0.001$) of apomorphine gnawing. The tyrosine hydroxylase inhibitor, α-methyltyrosine, significantly reduced potentiation of apomorphine gnawing by imipramine (Pedersen, 1968).

From the evidence it would appear that in addition to the dopaminergic mechanism, noradrenergic and serotoninergic mechanisms play a significant role in the potentiation of apomorphine induced gnawing by imipramine.

April 21, 1975

REFERENCES

CARLSSON, A., CORRODI, H., FUXE, K. & HOKFELT, T. (1969). *Eur. J. Pharmac.*, **5**, 357–366.
FRIEDMAN, E., SHOPSIN, B., GOLDSTEIN, M. & GERSHON, S. (1974). *J. Pharm Pharmac.*, **26**, 995–996.
PEDERSEN, V. (1967). *Acta. pharmac. tox.*, **25**, *Suppl.* 4, 63.
PEDERSEN, V. (1968). *Br. J. Pharmac.*, **34**, 219–220.
PLETSCHER, A., BROSSI, A. & GEY, K. F. (1962). *Int. Rev. Neurobiol.*, **6**, 275–306.
QUINN, G. P., SHORE, P. A. & BRODIE, B. B. (1959). *J. Pharmac. exp. Ther.*, **127**, 103–109.
THER, L. & SCHRAMM, H. (1962). *Archs int. Pharmacodyn. Thér.*, **138**, 302–310.